(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 026 298
A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 80104619.4

(22) Date of filing: 06.08.80

(51) Int. Cl.³: A 23 K 1/16
C 07 C 91/18, C 07 C 91/40
C 07 C 93/14

DERWS.

ANIMAL FEEDS CONTG. ~~SUBSTD.~~ PHENYL-ALKYLAMINE(S)+ FOR INCREASING GROWTH PROMOTION AND REDUCING FAT DEPOSITION

B C A O

(30) Priority: 16.08.79 US 66908
16.08.79 US 66909
24.04.80 US 143068
24.04.80 US 143078

(43) Date of publication of application:
08.04.81 Bulletin 81/14

(84) Designated Contracting States:
BE CH DE FR GB IT LI NL SE

(71) Applicant: American Cyanamid Company
1937 West Main Street
Stamford Connecticut 06904(US)

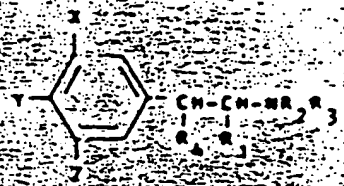
(72) Inventor: Kiernan, Jane Ann
620 Madison Avenue
Dunellen New Jersey(US)

(72) Inventor: Baker, Pamela Koenig
62 Hart Avenue
Hopewell New Jersey(US)

(74) Representative: Diehl, Hermann, Dr. et al,
Diehl & Kressin Fluggenstrasse 17
D-8000 München 19(DE)

(54) Method of making animal feed; preparations for promoting growth and reducing fat containing phenylethanolamine derivatives; phenylethanol amine derivatives.

(57) A method for the preparation of an animal feed composition comprising admixing an animal feed with from 0.01 to 400 grams per ton of feed of a compound of the following formula:



wherein X, Y, Z, R_1, R_2, R_3 and R_4 are as defined in the text. Some new compounds with the same general formula are claimed. These phenylethanol amine derivatives and their acid addition salts act as growth promotors and fat reducing agents in farm and companion animals.

EP 0 026 298 A1

27588D

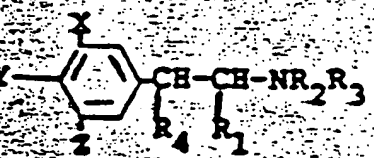
Croydon Printing Company Ltd.

TITLE MODIFIED
see front page

PHENYLETHANOLAMINE DERIVATIVES AND ACID ADDITION SALTS THEREOF USEFUL AS GROWTH PROMOTERS AND REDUCTION OF FAT IN FARM AND COMPANION ANIMALS

Substitution products of certain 1-(aminodihalophenyl)-2-aminoethanes and the acid addition salts thereof are disclosed in United States Patent 3,536,712, issued on October 27, 1970. Specifically, patentees disclose methods for the synthesis of said compounds and state that said compounds are useful for enhancing the blood circulation, and as bronchodilators, analgesics, sedatives, antipyretics, antiphlogistics and antitussives in warm-blooded animals. Patentees, however, exemplify only the analgesic utility. They do not indicate or suggest that said compounds are useful for lowering the deposition of fat or increasing the growth rate in worm-blooded animals, particularly farm and domestic animals, such as swine, poultry, dogs, sheep, goats, cats or cattle.

It has now been found that the growth rate and the depression of fat deposition of meat-producing animals such as swine, chickens, turkeys, domestic pets, rabbits, sheep, goats and cattle, including calves, can be increased and the efficiency of feed utilization thereby measurably improved by the oral or parenteral administration to said animals of an effective amount of a compound having the structure:



wherein X is hydrogen or halogen (fluorine, chlorine, iodine or bromine, but preferably chlorine or bromine; Y is hydrogen NH_2 or $NHCOR_5$; Z is H, halogen (fluorine, chlorine, iodine

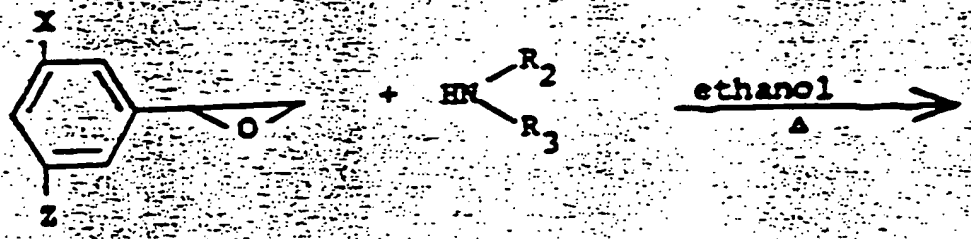
or bromine, but preferably chlorine or bromine) or OH; R_1 is hydrogen or C_1-C_4 alkyl; R_2 is hydrogen, C_1-C_4 alkyl (straight or branched-chain) or C_2-C_4 alkenyl; R_3 is hydrogen, C_1-C_6 alkyl (straight or branched-chain), C_3-C_6 cycloalkyl, methoxypropyl, C_2-C_5 alkenyl, phenyl, 2-hydroxyethyl, α,α-dimethylphenethyl or benzyl; and when R_2 and R_3 are taken together with the nitrogen to which they are attached, they may represent morpholino or N'-C_1-C_4 alkylpiperazino; R_4 is hydrogen, hydroxyl or OR_6; R_5 is hydrogen or C_1-C_4 alkyl; R_6 is C_1-C_6 alkyl; with the provisos that when R_3 is phenyl, 2-hydroxyethyl, α,α-dimethylphenethyl, cycloalkyl C_3-C_6, benzyl or methoxypropyl, R_2 is hydrogen; and when Z is OH, X and Y are hydrogen; and when Y is $NHCOR_5$, at least one of X and Z is hydrogen; and provided also that at least one of X,Y and Z represents a substituent other than hydrogen; racemic mixtures of the above-identified compounds and the optically active isomers and non-toxic, pharmacologically acceptable acid addition salts thereof.

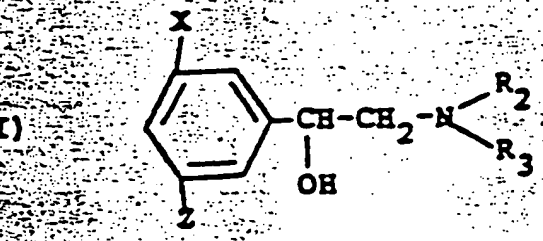
Preferred compounds for use in the method of this invention have the above structure wherein X and Z are each chlorine or bromine; Y is hydrogen or NH_2; R_1 is hydrogen or C_1-C_4 alkyl; R_4 is hydroxyl; or a non-toxic, pharmacologically acceptable acid addition salt thereof.

The most preferred compounds for use in enhancing the growth rate of meat-producing animals and for improving the efficiency of feed utilization thereby are: 4-amino-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol hydrochloride; 4-amino-3,5-dibromo-α-[(diisopropylamino)methyl]-benzyl alcohol hydrochloride; 4-amino-3,5-dichloro-α-[(diisopropylamino)methyl]benzyl alcohol hydrochloride; 4-amino-3,5-dibromo-α-[(tert-butylamino)methyl]-benzyl alcohol hydrochloride; 4-amino-3,5-dichloro-α-[(methylamino)methyl]-benzyl alcohol hydrochloride; 4-amino-3,5-dichloro-α-[(allylamino)methyl]benzyl alcohol; 4-amino-3-bromo-α-[(tert-butylamino)methyl]-5-chlorobenzyl alcohol hydrochloride; α-[4-amino-3,5-dichlorophenyl]-4-morpholineethanol hydrochloride; 4-amino-3-bromo-α-[(tert-butylamino)methyl]-5-

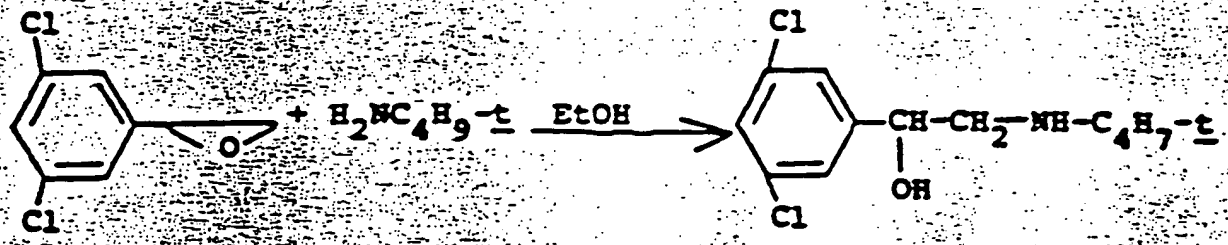
chlorobenzyl alcohol hydrochloride and α-[(tert-butylamino)-methyl]-3,5-dichlorobenzyl alcohol hydrochloride.

It is found, that formula (I) compounds below (wherein Y is hydrogen) can be prepared by the condensation of an appropriately substituted sytrene oxide with the appropriately substituted amine in the presence of an inert solvent, such as a lower alcohol at or near the boiling point of same, as shown below:



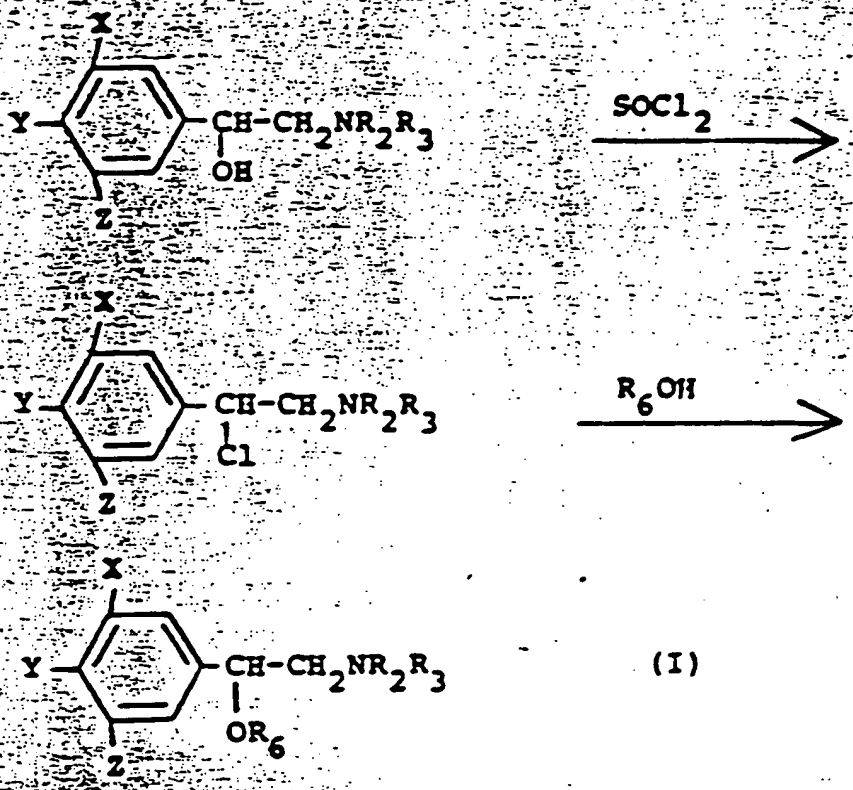


wherein X and Z are halogen, R_2 and R_3 are as hereinabove defined and Y is hydrogen. Thus, 3,5-dichlorostyrene oxide can be reacted with an equimolar or molar excess of t-butylamine in ethanol at reflux from about 1 to about 8 hours, or until the reaction is essentially complete and the desired α-[(t-butylamino)methyl]-3,5-dichlorobenzyl alcohol is obtained as illustrated below:



The thus obtained product can be purified by known procedures, such as chromatography or recrystallization of salt thereof.

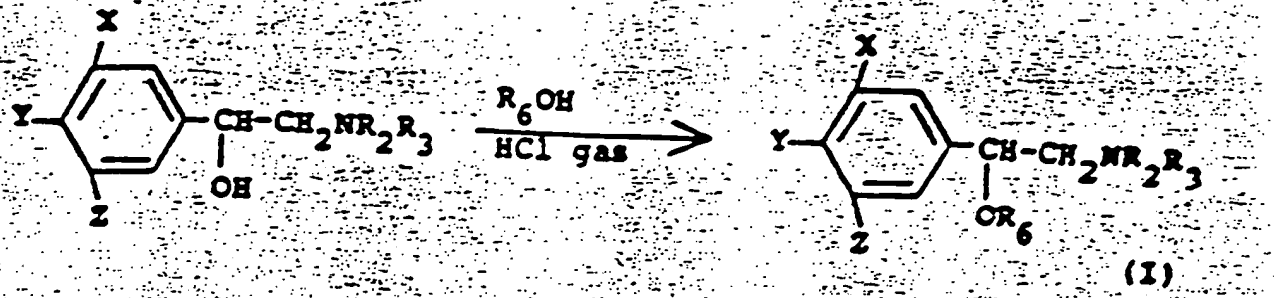
action.. The thus obtained halo compound is isolated by conventional laboratory methods and is then reacted with the appropriate alcohol, under an inert blanket of gas, such as nitrogen at a temperature range of from about 0 to 5°C. Thus thus obtained formula (I) product is then isolated by standard laboratory methods and purified, if so desired. The above reaction sequence may be graphically illustrated as follows:



(I)

wherein X,Y.Z,R_2,R_3 and R_6 are as hereinabove defined.

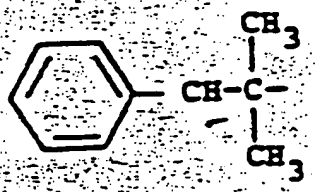
Alternatively, a formula (I) compound wherein R_4 is OR_6 may be prepared by dissolving the corresponding formula (I) compound wherein R_4 is OH in the corresponding R_6OH alcohol and saturating the thus obtained solution with dry HCl gas. The reaction mixture is then stirred at room temperature for a period of time sufficient to essentially complete the reaction and the product is then isolated by standard laboratory procedures and purified, if so desired. This reaction sequence may be illustrated as follows:



(I)

wherein X,Y,Z,R_2,R_3 and R_6 are as hereinabove defined.

In the present specification and claims the term α,α-dimethylphenethyl means a structure having the following configuration:



When orally administered in the feed, generally about 0.01 to 300 grams per ton of feed of the above-identified phenylethanolamine derivative or acid addition salt thereof, is effective for enhancing the growth rate and improving the efficiency of feed utilization by the above-mentioned meat-producing animals.

Since the effective and preferred dietary levels of the active ingredient vary somewhat from species to species in the above-mentioned animals said levels for each animal species are listed in Table I below on a gram per ton of feed basis:

Table I

Compound	Effective Feed Level g/ton	Preferred Level g/ton	Animal
Formula (I)	0.1-300	1-200	Swine
	0.1-200	1-100	Sheep, Goats
	0.01-50	0.1-10	Chickens, Rabbits
	0.01-50	0.1-10	Turkeys
	0.1-200	1-100	Cattle

Animal feed compositions which will provide the desired growth promotion and feed efficiency in the above-mentioned animals can be prepared by admixing the phenylethanolamine derivative or acid addition salt thereof, or an animal feed supplement containing said compound, with a sufficient quantity of an appropriate animal feed to provide the desired level of active compound in said feed.

Animal feed supplements can be prepared by admixing about 75% to 95% by weight of the phenylethanolamine derivative or acid addition salt thereof, with about 5% to 25% by weight of a suitable carrier or diluent. Carriers suitable for use to make up the feed supplement compositions include the following: alfalfa meal, soybean meal, cottonseed oil meal, linseed oil meal, sodium chloride, cornmeal, cane molasses, urea, bone meal, corncob meal and the like. The carrier promotes a uniform distribution of the active ingredient in the finished feed into which the supplement is blended. It thus performs an important function by ensuring proper distrubition of the active ingredient throughout the feed.

If the supplement is used as a top dressing for feed, it likewise helps to ensure uniformity of distribution of the active material across the top of the dressed feed.

For parenteral administration the phenylethanol-

amine derivative may be prepared in the form of a paste or pellet and administered as an implant, usually under the skin of the heat or ear of the animal in which enhanced growth rate and/or improved efficiency of feed utilization is sought.

In practive, parenteral administration generally involved injection of a sufficient amount of the above-said ethane derivative to provide the animal with from 0.001 to 100 mg/kg of body weight of the active ingredient. The preferred dosage level for swine is 0.01 to 50 mg/kg of body weight and for cattle the range of from 0.001 to 50 mg/kg of body weight of the active phenylethanolamine derivative is preferred. The preferred dose level of said ethane derivative for poultry is about 0.001 to 35 mg/kg of animal body weight and the preferred dose level of said ethanol derivative for sheep and goats is 0.001 to 40 mg/kg of animal body weight. The preferred dose level for rabbits and domestic pets is 0.001 to 35 mg/kg of animal body weight.

Paste formulations can be prepared by dispersing the active ethanol derivative in a pharmaceutically acceptable oil such as peanut oil, sesame oil, corn oil or the like.

Pellets containing an effective level of the phenylethanolamine derivative can be prepared by admixing the above-said active ingredient with a diluent such as carbowax, biodegradable polymers, carnuba wax, or the like. A lubricant, such as magnesium stearate or calcium stearate may be added to improve the pelleting process if desired.

It is, of course, recognized that more than one pellet may be administered to an animal to achieve the desired dose level which will provide the increased growth rate and/or improved efficiency of feed utilization by said animal. Moreover, it has been found that additional implants may also be introduced periodically during the treatment period in order to maintain the proper drug release rate in the animal's body.

In addition to enhanced growth promotion and improved efficiency of feed utilization by meat-producing animals, the compounds of the present invention have the add-

ed advantage that, at selected levels of administration they depress the deposition of fat in said animals. This biological response has substantial advantage to poultrymen and swine producers since administration of said compounds at selected levels yields leaner animals which command premium prices from the meat industry.

The invention has several advantages for the pet owner or veterinarian who wishes to trim unwanted fat from pet animals. For poultry men and swine raisers, using the method of the present invention were attained increased yields of leaner animals which command higher prices from the meat industry. Surprisingly, it is also noted that feed efficiency and animal growth rate are significantly enhanced when the compounds of the present invention are administered to swine and poultry at selected dose levels.

The following examples illustrate the invention.

Example 1

Evaluation of test compounds as animal growth promoters

CF1 female mice from Carworth Farms are received when they are six weeks old. They are housed ten to a cage in air-conditioned rooms (72°F to 76°F) with automatically controlled lights, 14 hours on and 10 hours off. The basal diet used in these studies is Purina Laboratory Chow (see description below), which is supplied ad libitum. Water is also allowed ad libitum.

Thirteen days after arrival, the mice are weighed in groups of ten and assigned at random to the different treatments. The concentration of the different compounds in the diet is indicated in the following tables. Twelve days later the mice are weighed again and the experiment terminated. Test data are provided in Table II below wherein data are reported as percentage gain over controls. The following is a description of the diet to which the growth-promoting compounds were added.

DIET

Guaranteed Analysis

Crude protein not less than	23.0%
Crude fat not less than	4.5%

1013 493

27523D

27588D

Crude fiber not more than	6.0%
Ash not more than	9.0%

Ingredients

Meat and bone meal, dried skimmed milk, wheat germ meal, fish meal, animal liver meal, dried beet pulp, ground extruded corn, ground oat groates, soybean meal, dehydrated alfalfa meal, cane molasses, animal fat preserved with BHA, vitamin B_{12} supplement, calcium pantothenate, choline chloride, folic acid, riboflavin supplement, brewer's dried yeast, thiamin, niacin, vitamin A supplement, D-activated plant sterol, vitamin E supplement, calcium carbonate, dicalcium phosphate, iodized salt, ferrec ammonium citrate, iron oxide, manganous oxide, cobalt carbonate, copper oxide, zinc oxide.

TABLE II

Evaluation of Test Compounds as Animal Growth Promoters

Dosage	Initial Mouse Wt. (g)	Final Mouse Wt. (g)	Gain (grams)	% Gain Over Control
4-Amino-α-(tert-butyl-aminomethyl)-3,5-dichlorobenzyl alcohol hydrochloride				
(ppm in diet)				
0	23.46	24.67	1.21	
	23.46	24.49	1.03	
	22.79	24.62	1.83	
	24.10	25.98	1.88	
	24.23	25.52	1.29	
	23.63	24.93	1.30	
	23.33	24.76	1.43	
	22.75	23.86	1.11	
Control Average	23.47	24.85	1.39	6% ↑

5.92

1015

27588D

495

TABLE II (Continued)

Evaluation of Test Compounds as Animal Growth Promoters

Dosage	Initial Mouse Wt. (g)	Final Mouse Wt. (g)	Gain (grams)	% Gain Over Control
50	22.95	25.63	2.68	
	23.91	26.14	2.23	
	24.26	26.30	2.04	
Average	23.71	26.02	2.32	+66.9
100	23.50	25.39	1.89	
	23.80	26.04	2.24	
	23.00	25.65	2.65	
Average	23.43	25.69	2.26	+62.6
200	23.03	24.80	1.77	
	24.50	26.12	1.62	
	23.08	25.04	1.96	
Average	23.54	25.32	1.78	+28.1

7.6% 1.56

The procedure described above is repeated using control animals for each test. Twelve days after the tests are started the animals are weighed and the test terminated. The results of each test are reported in Table III below as weight gains for each test group and percent gain for each group over controls.

TABLE III

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
4-Amino-3,5-dibromo-α-[(tert-butylamino)methyl]-benzyl alcohol hydrochloride	400	16.5	+22.2
	200	20.4	+51.1
	100	22.9	+69.0
	50	23.3	+72.6
4-Amino-3,5-dibromo-α-[(diisopropylamino)methyl]-benzyl alcohol hydrochloride	200	20.2	+46.4
	100	16.9	+22.5
P-amino-α-[(dimethylamino)methyl]benzyl alcohol	200	17.6	+28.3
	100	15.6	+13.0
P-amino-α-[(diisopropylamino)methyl]benzyl alcohol hydrochloride	200	16.5	+18.7
	100	14.2	+ 2.2
4-Amino-3,5-dichloro-α-[(dimethylamino)methyl]benzyl alcohol hydrochloride	100	18.4	+ 7.6
4-Amino-3,5-dichloro-α-[(diisopropylamino)methyl]-benzyl alcohol hydrochloride	200	23.9	+66.0
	100	21.3	+47.9

TABLE III (Continued)

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
4-Amino-3,5-dichloro-α-[(cyclohexylamino)methyl]-benzyl alcohol hydrochloride	200	19.3	+48.5
	100	16.3	+25.4
P-amino-α-[(tert-butylamino)methyl]benzyl alcohol	200	19.6	+88.5
	100	18.2	+75.0
	50	17.9	+72.1
	25	13.6	+30.8
4-Amino-3,5-dichloro-α-[(methylamino)methyl]benzyl alcohol hydrochloride	200	15.6	+54.5
	100	18.9	+87.1
P-amino-α-[(methylamino)methyl]benzyl alcohol hydrochloride	100	14.8	+18.4
α-(4-Amino-3,5-dichlorophenyl)-4-morpholineethanol hydrochloride	200	15.9	+34.7
	100	14.0	+18.6
4-Amino-α-[(sec-butylamino)methyl]-3,5-dichloro-benzyl alcohol	200	13.2	+16.8

TABLE III (Continued)

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
4-Amino-3,5-dichloro-α-[(-3-methoxypropyl)amino]-methyl benzyl alcohol	200	15.4	+23.2
	100	23.0	+84.0
4-Amino-3,5-dichloro-α-[(diallylamino)methyl]benzyl alcohol hydrochloride	200	17.4	+39.2
	100	18.4	+47.2
4-Amino-3,5-dichloro-α-[(benzylamino)methyl]benzyl alcohol hydrochloride	200	10.6	+19.1
4-Amino-α-[(butylamino)methyl]-3,5-dichlorobenzyl alcohol	100	14.6	+64.0
4-Amino-3,5-dichloro-α-[(4-methyl-1-piperazinyl)-methyl]benzyl alcohol	200	9.4	+ 5.6
	100	9.5	+ 6.7
4-Amino-3,5-dichloro-α-[(isopropylamino)methyl]-benzyl alcohol	200	13.1	+26.0
	100	18.9	+81.7

TABLE III (Continued)

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
4-Amino-α-(aminomethyl)-3,5-dichlorobenzyl alcohol hydrochloride	100	13.4	+19.0
4-Amino-3,5-dichloro-α-[(hexylamino)methyl]benzyl alcohol	200 100	16.8 19.2	+15.9 +32.8
α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol hydrochloride	200 100	19.3 20.2	+33.1 +39.3
4-Amino-3,5-dichloro-α-[(diethylamino)methyl]benzyl alcohol hydrochloride	100	17.5	+20.7
α-[(allylamino)methyl]-4-amino-3,5-dichlorobenzyl alcohol	200 100	16.8 17.1	+118.2 +122.1
4-Amino-α-(anilinomethyl)-3,5-dichlorobenzyl alcohol	200 100	20.7 17.5	+25.5 + 6.1

TABLE III (Continued)

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
4-Amino-α-[1-tert-butylamino)ethyl]-3,5-dichloro-benzyl alcohol hydrochloride	200	22.7	+37.6
	100	23.8	+44.5
4-Amino-3-bromo-α-[(tert-butylamino)methyl]-5-chloro-benzyl alcohol hydrochloride	200	18.5	+60.9
	100	19.5	+69.6
α-[(tert-butylamino)methyl]-m-hydroxybenzyl alcohol hydrochloride	200	15.8	+ 9.0
	100	19.9	+37.2
α-[(isopropylamino)methyl]-m-hydroxybenzyl alcohol hydrochloride	400	-	+54.4
	200	-	+53.0
	100	-	+39.7
α-[(Amino)methyl]-m-hydroxybenzyl alcohol hydrochloride	200	-	+ 4.4
	100	-	+30.7
4-Amino-N-tert-butyl-3,5-dichloro-β-methoxyphenethyl hydrochloride	200	18.8	+37.2
	50	21.6	+57.7

Example 2

Evaluation of test compounds as animal growth promoters

The procedure of Example 1 is used in this evaluation. The diet is the same as described in said example 5 and data obtained are reported as percent gain over controls. Data are reported in Table IV below.

TABLE IV

Evaluation of Test Compounds as Animal Growth Promoters

Dosage	Initial Wt. (g)	Final Wt. (g)	Gain (grams)	% Gain Over Control
4-Amino-α-(tert-butylaminomethyl)-3,5-dichlorobenzyl alcohol hydrochloride				
(ppm in diet)				
0	24.49	25.17	.68	
	24.25	26.06	1.81	
	23.65	25.43	1.78	
	22.83	24.33	1.50	
	24.39	25.59	1.20	
	24.36	26.06	1.70	
	23.11	24.50	1.39	
	23.54	24.82	1.28	
Average	23.83	25.25	1.42	-

TABLE IV (Continued)

Evaluation of Test Compounds as Animal Growth Promoters

Dosage	Initial Wt. (g)	Final Wt. (g)	Gain (grams)	% Gain Over Control
200	23.46	25.49	2.03	
	23.68	25.97	2.37	
	23.56	25.40	1.84	
Average	23.57	25.62	2.05	+44.4

Iodine	1.7%
Cobalt	0.2%
Calcium minimum 15.3%	1.2%
Calcium maximum 17.3%	

**Vitamin Premix for 1-ton

	Weight in Gram
DL Methionine	453.6
BHT (butylated hydroxy toluene)	113.6
Vitamin A (30,000 mcg/g)	100.0
Vitamin D_3 (200,000 mcg/g)	5.0
Vitamin E (20,000 mcg/lb)	45.4
Riboflavin	4.0
Niacinamide	23.0

TABLE V

Mean Weight Gain and Feed Efficiency of Control and Test Compound - Treated Chicks

Thirteen-Day Battery Testing

Treatment	ppm in Diet	Mean Gain (g)	% Control	F/G	% Improvement over Control
Control	0	266.5	-	1.40	-
4-Amino-α-[(tert-butylamino)methyl] 3,5-dichlorobenzyl alcohol	0.3	271.8	+2.0	1.40	0
	0.6	274.3	+2.9	1.38	+1.4
	1.25	259.9	-2.5	1.41	-0.7
	2.5	260.8	-2.1	1.39	+0.7
	5.0	251.9	-5.5	1.40	0
4-Amino-3,5-dibromo-α-[(tert-butyl-amino)methyl]benzyl alcohol hydrochloride	0.3	270.8	+1.6	1.40	0
	0.6	271.8	+2.0	1.38	+1.4
	1.25	267.5	+0.4	1.39	+0.7
	2.5	265.2	-0.5	1.38	+1.4
	5.0	270.3	+1.4	1.37	+2.1

Example 4

Evaluation of test compounds as antilipogenic agents - Mouse tests

CFI female mice from Carworth Farms are received when they are six weeks old. They are housed ten to a cage in air-conditioned rooms (72°F to 76°F) with automatically controlled lights, 14 hours on and 10 hours off. The basal diet used in these studies is Purina Laboratory Chow (see description below), which is supplied ad libitum.

The following is a description of the diet to which the growth-promoting compounds were added.

DIET

Guaranteed Analysis

Crude protein not less than	23.0%
Crude fat not less than	4.5%
Crude fiber not more than	6.0%
Ash not more than	9.0%

Ingredients

Meat and bone meal, dried skimmed milk, wheat germ meal, fish meal, animal liver meal, dried beet pulp, ground extruded corn, ground oat groats, soybean meal, dehydrated alfalfa meal, cane molasses, animal fat preserved with BHA, vitamin B_{12} supplement, calcium pantothenate, choline chloride, folic acid, riboflavin supplement, brewer's dried yeast, thiamin, niacin, vitamin A supplement, D-activated plant sterol, vitamin E supplement, calcium carbonate, dicalcium phosphate, iodized salt, ferric ammonium citrate, iron oxide, manganous oxide, cobalt carbonate, copper oxide, zinc oxide. Water is also allowed ad libitum.

Thirteen days after arrival, the mice are weighed in groups of ten and assigned at random to the different treatments. The concentration of the different compounds in the diet is indicated in the following tables. Twelve days later the mice are weighed again the experiment terminated. At least three cages (30 mice) of untreated controls are included in each test. Test data are provided in Table VI below wherein data are reported as percent body fat, percent change in body fat from controls and gain per mouse

TABLE V

Antilipogenic Agent Evaluation and Growth Enhancement Evaluation in Mice

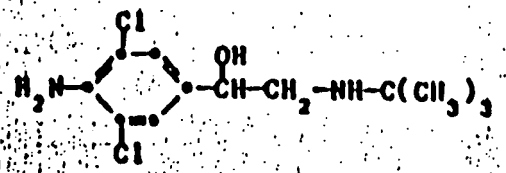
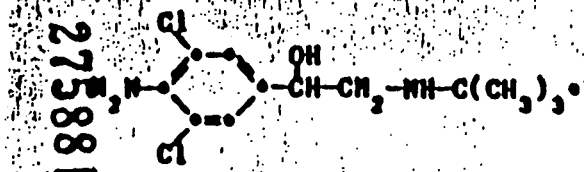
Compound	Level in Diet (ppm)	Number of Mice per Treatment	Average Initial Weight (g)	Average Final Weight (g)	Gain per House (g)	% Body Fat	Change in % Fat from Control
	0	50	23.6	25.0	1.4	11.95	-
	50	30	23.7	26.0	2.3	11.95	0
	100	30	23.4	25.7	2.3	10.23	-14.40
	200	30	23.5	25.3	1.8	10.50	-12.13
	400	30	23.4	24.9	1.4	9.10	-23.80

TABLE VI

Antilipogenic Agent Evaluation and Growth Enhancement Evaluation in Mice

Compound	Level in Diet (ppm)	Number of Mice per Treatment	Average Initial Weight (g)	Average Final Weight (g)	Gain per House (g)	Percent Body Fat	Change in Fat from Control
	0	50	23.6	25.0	1.4	11.95	-
	50	30	23.7	26.0	2.3	11.95	0
	100	30	23.4	25.7	2.3	10.23	-14.40
	200	30	23.5	25.3	1.8	10.50	-12.13
	400	30	23.4	24.9	1.4	9.10	-23.80

Percent Body Fat Determination of Mice

A. Preparation of Carcasses:

Stomach and intestines are removed from each mouse. All other viscera, including skin and fur, remain intact. Each cage of mice (10) are weighed and added to a 1000 ml beaker and autoclaved at 120°C (15 psi) for 30 minutes. Carcasses from each cage are then blended and homogenized. The homogenate is weighed and duplicate 5-gram samples are removed for analysis.

B. Fat Analysis:

Fifteen milliliters (ml) of concentrated hydrochloric acid is added to each 5-gram sample and mixed well. Samples are heated in an 84°C water bath for 2 hours. To extract the fat, thirty ml of petroleum ether is added to each samples, 15 ml at a time, and mixed well on a Vortex mixer. The aqueous and organic phases are separated by low speed centrifugation and the ether layer (containing fat) is extracted into tared 30 ml beakers. After evaporating to dryness the beaker containing fat is reweighed to determine grams of fat per five grams of homogenate. Total body fat in the carcass is calculated as follows:

$$\% \text{ Fat} = \frac{\left[\begin{matrix}\text{grams fat} \\ \text{in sample}\end{matrix}\right] \quad \left[\begin{matrix}\text{grams total} \\ \text{homogenate}\end{matrix}\right]}{\left[\begin{matrix}\text{gram weight} \\ \text{of sample}\end{matrix}\right] \quad \left[\begin{matrix}\text{carcass weight} \\ \text{of mice (g)}\end{matrix}\right]} \times 100$$

Example 5

Antilipogenic Evaluation of test compounds - Mouse Study

CFI female mice, 55 days old, are weighed in groups of 10 and allotted to cages to minimize weight variation among cages. Treatments are randomly assigned to cages.

Each of the treatments are tested in 3 replicates, i.e., in 3 cages of 10 mice each. There are 10 cages of 10 control mice each. Durgs are mixed in the diet at the dosage level indicated. Feed and water are offered ad libitum for the 12-day test period. Feed spilled is collected during the test period. At the end of the test period, the collected feed is weighed and the mean feed consumption per cage of ten

mice is determined for each treatment. The mice are weighed as a group of 10 and the weight gain determined. The mice are sacrificed by cervical dislocation. The right uterine fat pad of each mouse is removed. The fat pads for each cage of 10 mice are weighed as a unit.

To establish correlation between the percent reduction in fat pad weights of treated animals and percent reduction in total body fat of treated animals, animals from several treatment groups are evaluated for total body fat using the body fat determination described in Example 5. Data obtained are reported in Table VII for those groups upon which such determination has been made. From percent reduction in fat pad weight and the total fat determinations for the groups tested, it can be seen that a reduction in fat pad weights of animals is generally indicative of a reduction of total body fat of the treated animals.

TABLE VII

Antilipogenic Evaluation of Test Compounds - Mouse Study

Compound	Dosage (ppm)	% Reduction in Fat Pad Weight vs Controls	% Animal Fat vs Controls
4-amino-3,5-dibromo-α-[(tert-butylamino)methyl]benzyl alcohol hydrochloride	400	-21.4	-14.6
	200	-27.5[a]	-18.4[a]
	100	-13.9[a]	- 5.3[a]
4-amino-3,5-dibromo-α-[(diisopropylamino)methyl]benzyl alcohol hydrochloride	200	-11.1	- 9.4
4-amino-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol hydrochloride	400	-50.0	-23.8
	200	-28.1	-12.1
	100	-37.9	-14.4
4-amino-3,5-dichloro-α-[(methylamino)methyl]benzyl alcohol hydrochloride	200	-14.7	- 9.9
	100	- 8.8	-11.5
4-amino-3,5-dichloro-α-[(diethyl)methyl]benzyl alcohol hydrochloride	200	-64.7	
	100	-41.2	
4-amino-α-[(sec-butylamino)methyl]-3,5-dichlorobenzyl alcohol	200	-56.2	-36.3
	100	-18.2	-19.3

[a]Average 2 tests

TABLE VII (Continued)

Antilipogenic Evaluation of Test Compounds - House Study

Compound	Dosage (ppm)	% Reduction in Fat Pad Weight vs Controls	% Animal Fat vs Controls
4-amino-3,5-dichloro-α-[(diallylamino)methyl] benzyl alcohol hydrochloride	200	-12.0	
4-amino-3,5-dichloro-α-[(benzylamino)methyl]benzyl alcohol hydrochloride	200	-17.7	- 5.4
	100	-21.1	- 1.7
4-amino-α-[(butylamino)methyl]-3,5-dichlorobenzyl alcohol	200	-21.54	-16.78
	100	-24.7	-13.08
4-amino-3,5-dichloro-α-[(isopropylamino)methyl]benzyl alcohol	200	-50.2	-25.5
	100	-36.9	-20.4
α-[(allylamino)methyl]-4-amino-3,5-dichlorobenzyl alcohol	200	-16.5	
	100	-18.3	
4-amino-α-[1-(tert-butylamino)ethyl]-3,5-dichlorobenzyl alcohol hydrochloride	100	-18.8	
α-[(t-butylamino)methyl]-3,5-dichlorobenzyl alcohol hydrochloride	200	-22.5	
	100	-14.8	

TABLE VII (continued)

Antilipogenic Evaluation of Test Compounds - Mouse Study

Compound	Dosage (ppm)	% Reduction in Fat Pad Weight vs Controls	% Animal Fat vs Controls
4-amino-3-bromo-α-[(t-butylamino)methyl]-5-chloro-benzyl alcohol hydrochloride	200	-17.8	
	100	-18.7	
m-hydroxy-α-[(isopropylamino)methyl]benzyl alcohol	400	-19.8	
	200	-26.2	
	100	- 7.5	
4-amino-N-t-butyl-3,5-dichlorophenethylamine hydrochloride	50	-24.8	
4-amino-3,5-dichloro-α-[(cyclopropylamino)methyl]-benzyl alcohol	100	-30.7	
4-[2-(t-butylamino)-1-hydroxyethyl]-2'-chloroacetanilide	200	- 6.7	
	100	-12.1	
4-amino-3,5-dichloro-α-[(cyclopentylamino)methyl]benzyl alcohol	200	-24.5	
	50	- 4.7	
4-amino-3,5-dichloro-α-[[(2-hydroxyethyl)amino]methyl]-benzyl alcohol	200	-15.2	
	50	- 7.4	
4-amino-α-[(t-butylamino)methyl]-3,5-diiodobenzyl alcohol hydrochloride	200	-32.6	
	100	-26.6	
4-amino-N-t-butyl-3,5-dichloro-β-methoxyphenethylamine hydrochloride	200	-13.4	
	50	-21.7	

Example 7

Antilipogenic evaluation of test compounds - Rat study

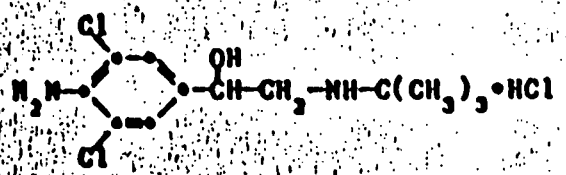
The procedure employed and the diet used for evaluation of test compounds as antilopogenic agents mice, are described in Example 1, excepting that the treatment period is fourteen days and 10 rats, one per cage, are used for each treatment.

Percent body fat is determined in the same manner as described in Example 4, excepting that the skin and organs are removed before the carcasses are homogenized.

Results of this study are reported in Table VIII below.

TABLE VIII

Antilipogenic Evaluation of Test Compounds and Growth Rate Evaluation in Rats

Compound	Level in Diet (ppm)	Number of Rats per Treatment	Average Initial Weight (g)	Average Final Weight (g)	Average Gain per Rat (g)	% Fat in Eviscerated Carcass	Change in Fat from Control
	0	10	72.7	149.1	76.4	4.67	-
	25	10	78.3	159.3	81.0	3.04	-34.9
	100	9	76.6	159.8	83.2	2.54	-42.0
	400	10	73.2	146.4	73.2	2.71	-45.6

EXAMPLE 8

Evaluation of test compounds as animal feed additives for the enhancement of growth rate and improvement in feed efficiency of mice.

Four-week old female outbred rats (5-gram range) from Charles River Breeding Laboratories, 251 Ballardvale Street, Wilmington, Massachusetts 01887, are housed 2/cage in air-conditioned rooms (72°F to 76°F) with automatically controlled lights, 14 hours on and 10 hours off. The basal diet used in these studies is Purina Laboratory Chow which is supplied ad libitum. Water is also given ad libitum.

Four days after arrival, the animals are weighed and allotted to treatment groups to minimize weight variation. Ten rats are used per treatment group. Drugs are administered in the feed at 2 ppm, 10 ppm and 50 ppm for a period of 12.5 weeks. Animals are weighed weekly and feed consumption corrected for spillage recorded daily. The results of this trial are shown below in Table IX.

TABLE IX

Evaluation of Test Compounds as Animal Feed Additives for the Enhancement of Growth Rate and Improvement in Feed Efficiency - Mice

Treatment	Dose ppm	Gain[a] (g)	Feed Consumption[b] (g)	Feed/Gain % Improvement
Control		157	1304	8.31
4-Amino-α-(tert-butylaminomethyl)-3,5-dichloro-benzyl alcohol hydrochloride	2	178 (+13.4%)	1443 (+10.7%)	8.11 (+2.4%)
	10	186 (+18.5%)	1467 (+11.5%)	7.89 (+5.1%)
	50	175 (+11.5%)	1394 (+6.9%)	7.97 (+4.1%)
4-Amino-3,5-dibromo-α-[(tert-butylamino)methyl]-benzyl alcohol hydrochloride	2	164 (+4.5%)	1362 (+4.5%)	8.3 (0.1%)
	10	185 (+7.8%)	1459 (+11.9%)	7.89 (+5.1%)
	50	184 (+17.2%)	1416 (+8.6%)	7.70 (+7.3%)

[a]Values given are the total average gain (g) per rat for the entire experimental period.

[b]Values given are the total average feed consumed per rat for the entire experimental period.

Figures in parentheses are % improvement over control.

EXAMPLE 9

α-[(Tert-butylamino)methyl]-3,5-dichlorobenzyl Alcohol Hydrochloride

A solution containing 3.5 g of 3,5-dichlorostyrene oxide in 50 ml of absolute ethanol and 20 ml of t-butylamine is heated gently at reflux for 8 hours and the mixture is evaporated to dryness. The clear yellow syrup is dissolved in 75 ml of ethanol and 25 ml of H_2O, and the solution is cooled to 5°C and acidified with 3N HCl. This solution is evaporated to dryness in vacuo and the residual white solid is recr-stallized from acetone to afford 2.81 g, m.p. 218-221°C.

Anal. Called for $C_{12}H_{17}NOCl_2HCl$: C, 48.26; H, 6.08; N, 4.69. Found: C, 48.49; H, 6.17; N, 4.66.

The free base of the title compound is obtained by neutralization of the title compound with aqueous 10% NaOH. Other salts of the free base are then obtained by treatment of the free base in the above-mentioned procedure (aqueous ethanol) with addition of the appropriate acids, such as H_2SO_4, H_3PO_4, HNO_3, CH_3SO_3H, toluenesulfonic acid and pamoic acid.

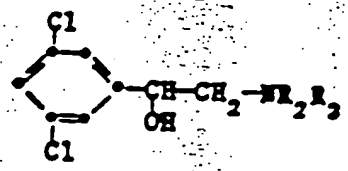
The intermediate 3,5-dichlorostyrene oxide needed for preparing the title compound is made by reducing 28.4g of 3,5-dichlorophenacyl bromide in 125 ml of absolute ethanol at 5°C with 8g of $NaBH_4$, added portionwise. After the addition is completed, the reaction mixture is stirred 16 hours at ambient temperature, which is obtained by gradual melting of the ice bath overnight. The mixture is quenched with 100 ml of H_2O, the aqueous mixture is cooled to 5°C, and carefully acidified to pH 3 with concentrated HCl. The mixture is extracted with 300 ml of CH_2Cl_2 and the extract is dried over $MgSO_4$, filtered, and evaporated to dryness in vacuo to afford the epoxide as a clear yellow oil.

The phenacyl bromide intermediate for the above-mentioned styrene oxide is prepared by brominating 10 g of 3,5-dichloroacetophenone in 50 ml of $CHCl_3$/50 ml of EtOAc with 23.6 g of $CuBr_2$. The mixture is heated at reflux for

2.5 hours and cooled to room temperature. After stirring for 16 hours at room temperature, the mixture is cooled in ice for 2 hours and filtered. The filter cake is washed with 50 ml of $CHCl_3$ and the combined filtrates are twice decolorized with activated carbon, filtered, and evaporated to dryness *in vacuo* to afford the orange oil of the 3,5-dichlorostyrene oxide.

EXAMPLE 10

The following 3,5-dichlorophenyl compounds (A) related to the title compound of Example 9 are prepared by the method described in Example 6 by substituting t-butyl amine with R_2R_3NH amines.



A

Compound	R_2	R_3
1	H	H
2	H	CH_3
3	H	C_2H_5
4	H	i-C_3H_7
5	H	n-C_3H_7
6	H	n-C_6H_{13}
7	H	cyclohexyl
8	H	CH_2-CH=CH_2
9	H	CH_2-CH=CH-CH_3
10	H	CH_2C=CH

A (Continued)

Compound	R_2	R_3
11	H	phenyl
12	H	methoxypropyl
13	H	benzyl
14	CH_3	CH_2
15	C_2H_5	C_2H_5
16	$CH_2CH=CH_2$	$CH_2CH=CH_2$
17	i-C_3H_7	i-C_3H_7
18	$CH_2-CH=CH_2$	$-CH_2-CH=CH_2$
19	H	cyclopropyl
20	$-CH_2-CH_2-O-CH_2-CH_2-$	
21	H	n-butyl
22	H	$C(CH_3)_2-CH_2$ 

EXAMPLE 11

α-[(Tert-butylamino)methyl]-3,5-dibromobenzyl Alcohol Hydrochloride

This title compound is prepared from 3,5-dibromostyrene oxide in the same manner as described in Example 9. The starting materials for this styrene oxide are similarly prepared starting with 3',5'-dibromoacetophenone.

The corresponding α-[(isopropylamino)methyl]-3,5-dibromobenzyl alcohol hydrochloride is prepared by substituting isopropyl amine for t-butyl amine.

EXAMPLE 12

m-Hydroxy-α-[(isopropylamino)methyl]benzyl Alcohol Hydrochloride

In 135 ml of 95% ethanol, 36.75 g of m-hydroxyacetophenone, 36.5 g of benzyl chloride, 1.75 g of KI, and 24.6 g of K_2CO_3 are stirred and heated at reflux for 5 hours. The mixture is cooled, evaporated in vacuo to remove ethanol and 100 ml of H_2O is added. The mixture is then extracted with diethyl ether three times to afford 350 ml of extract, which is further washed with 50 ml of H_2O, saturated $NaHCO_3$ solu-

tion (2 x 50 ml), 50 ml of H_2O, and 50 ml of brine in succession. The filtrate is dried over Na_2SO_4 and evaporated to dryness. The residual oil is distilled to afford 49.13 g of m-benzyloxyacetophenone, b.p. 145-147°C/0.2 mm. Bromination of 186 g of this acetophenone is accomoplished with 349 g of $CuBr_2$ in 1ℓ of $CHCl_3$/1.5 ℓ of ethanol heated at reflux. A N_2 sweep is used to remove HBr generated. After 4 hours, the mixture is filtered and the filter cake is washed with $CHCl_3$ (2 x 100 ml). The filtrate is evaporated *in vacuo* to afford an oil, which is dissolved in 200 ml of absolute ethanol (2 x 50 ml), and dried to afford 64.28g m-benzyloxyphenacyl bromide, m.p. 57-58°C. Further cooling of the filtrate affords 34g. A 64 g-sample of the phenacyl bromide is added to a stirred mixture containing 212 ml of i-propylamine in 425 ml of ethanol under N_2 atmosphere at 5°C. The temperature rises to 12°C and a clear solution is obtained. The solution is poured into ice (2 L) containing 500 ml of concentrated HCl and 1500 ml of H_2O. After stirring for 20 minutes, the mixture is filtered and the solid is washed with H_2O. On drying this gives 98.64g, m.p. 200-203°C dec. This solid is dissolved in 400 ml of refluxing methanol, 400 ml of isopropyl alcohol is added, and the solution is concentrated to 400 nl. On cooling and collecting crystals, 54.36 of ketoamine melting at 213-215° dec is obtained. This material (16 g) is added to 150 ml of methanol which contains 2 g of 5% Pd/carbon and hydrogenated in a Paar vessel at 42 p.s.i.g. of H_2. The mixture is filtered and the filtrate is evaporated. The residue is mixed with 50 ml of isopropyl alcohol and evaporated to dryness to afford a syrup, which is mixed with 100 ml of ethanol. They crystals are collected, washed with diethyl ether and dried to give 10.77 g, m.p. 129-132°C, of the title compound.

By substituting tert-butylamine for isopropylamine, m-hydroxy-α-[(tert-butylamino)methyl]benzyl alcohol hydrochloride, m.p. 150-154°C dec. is obtained. Substitution of isopropylamine with diisopropylamine, benzylamine and allylamine affords m-hydroxy-α-[(diisopropylamino)methyl]-

benzyl alcohol, m-hydroxy-α-[(benzylamino)methyl]benzyl alcohol, and m-hydroxy-α-[(allylamino)methyl]benzyl alcohol hydrochlorides, respectively.

EXAMPLE 13

4-Amino-α[(tert-butylamino)methyl]-3,5-diiodobenzyl Alcohol Hydrochloride

In 10 ml of acetic acid, 0.42 g of p-amino-α-[(tert-butylamino)methyl]benzyl alcohol is stirred under N_2 atmosphere and 0.48g of N,N-dichlorobenzenesulfonamide and 0.6g of NaI are stirred under N_2 atmosphere for 20 minutes. After 3 days, the mixture is poured into ice and the mixture is basified with 50% aq. NaOH. This mixture is extracted with CH_2Cl_2 (3 x 25 ml) and chromatographed on a SiO_2 plate using 1% NH_4OH/20% CH_3OH/CH_2Cl_2 to afford 0.22g of the title compound. The reaction is repeated on a larger scale (8X) and the eluted crude product is dissolved in 100 ml of ethanol/10 ml of H_2O, stirred and 10% HCl is added to give pH 3. The mixture is evaporated to dryness in vacuo. Isopropyl alcohol is added and the mixture is evaporated to dryness. This process is repeated twice and the residue is crystallized from methanol/isopropyl alcohol by allowing methanol to evaporate until crystals from (methanol is used to dissolve the crude material before isopropyl alcohol is added). On cooling, 2g of the title compound is obtained melting at 187°C dec.

Anal. Calc'd for $C_{12}H_{19}ClI_2N_2O$: C,29.02; H,2.86; N,5.64.
Found: C, 29.11; H, 3.64; N, 5.64.

EXAMPLE 14

α-[(Tert-butylamino)methyl]-3,5-dichlorobenzyl Alcohol Hydrochloride

An alternate procedure for preparing the title compound and the compounds described in Example 9 is exemplified. Thus, 10 g of 4-amino-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol is added to 100 ml of 50-52% H_3PO_2 and the mixture is stirred and cooled to 8°C in ice while 2.77 g of $NaNO_2$ in 15 ml of H_2O is added over 65 minutes. Foaming occurs and is controlled with antifoaming silicone.

After 20 minutes, the mixture is stirred 2 hours without cooling. The mixture is then poured into ice-H_2O mixture and 50% aq. NaOH solution is added until the mixture is alkaline. The alkaline mixture is extracted with CH_2Cl_2 three times to give 200 ml of solution, which is washed with 25 ml of 2% NaOh and dried over $MgSO_4$ and evaporated to dryness in vacuo to give 9.13 g of brown oil. On standing, the oil solidifies, and it is dissolved in 100 ml of ethanol containing 10 ml of H_2O. The solution is acidified to pH 3 with 10% HCl and evaporated to dryness. The residue is treated with 50 ml of isopropyl alcohol and evaporated to dryness. This procedure is repeated to afford an off-white solid which is dissolved in methanol. The solution is evaporated in vacuo to afford a syrup, which is diluted with 50 ml of isopropyl alcohol and allowed to stand. The crystals which form are collected, washed with isopropyl alcohol and dried to yield 7.8 g, m.p. 217-221°C dec., of the title compound.

The compound described in Example 6 is similarly prepared. Deamination of 4-amino-3,5-dibromo-α-[(tert-butylamino)methyl]benzyl alcohol affords 3,5-dibromo-α-[(tert-butylamino)methyl]benzyl alcohol, m.p. 249-251°C dec.

EXAMPLE 15

4-Amino-3,5-dichloro-β-methoxyphenethylamine hydrochloride

Under N_2 atmosphere, 11 g of 4-amino-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl chloride is added to 75 ml of methanol at 0°C. After 20 minutes, the cooling bath is removed and the reaction mixture is stirred at ambient temperature. After the reaction is completed, the mixture is evaporated to dryness in vacuo. The residue is stirred in 75 ml of H_2O and the mixture is made alkaline with 6N NaOH solution and extracted with CH_2Cl_2 (3 x 50 ml). The organic phases are dried over $MgSO_4$ and evaporated to dryness to afford an orange oil. This oil is dissolved in 150 ml of absolute EtOH and acidified with HCl/isopropyl alcohol solution to pH 2. The solution is evaporated to dryness and the residue is stirred in 75 ml of ethyl acetate. After cooling, this affords a pale yellow solid which is collected to give

6.97 g of the title compound, m.p. 195-198°C dec.

Similarly, substitution of ethyl alcohol, isopropyl alcohol, n-butyl alcohol and n-hexyl alcohol affords the corresponding β-ethoxy, β-isopropoxy, n-butoxy, and n-hexyloxy phenethylamine hydrochlorides.

EXAMPLE 16

4-Amino-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl chloride

Under N_2 atmosphere, 27.72 g of 4-amino-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol is added to 200 ml of thionyl chloride stirred at 0-5°C. After addition is completed, the reaction mixture is stirred at ambient temperature for 3 hours. Subsequently, the mixture is evaporated to dryness in vacuo to afford 37.34 g of yellow solid, which is used as is.

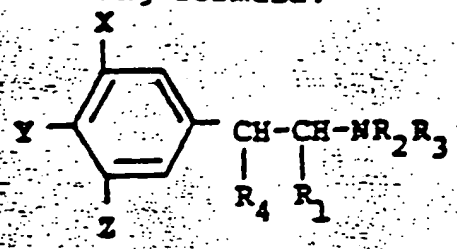
EXAMPLE 17

Alternate Procedure for 4-Amino-3,5-dichloro-β-methoxyphenethylamine hydrochloride

I. 100 ml of methanol, 10 g of 4-amino-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol is stirred in an ice bath and dry HCl gas is introduced into the solution. After saturation of the solution, the mixture is stirred at room temperature for an hour and evaporated to dryness. The solid is then stirred in ethyl acetate to afford the title product, which is collected by filtration.

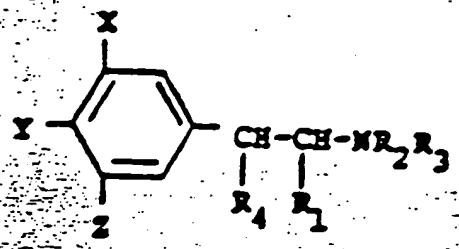
CLAIMS

1. An Animal feed composition comprising a balanced diet and from 0.01 to 400 grams per ton of feed of a compound of the following formula:



wherein X is hydrogen or halogen (fluorine, chlorine, iodine or bromine, but preferably chlorine or bromine); Y is hydrogen, NH_2 or $NHCOR_5$; Z is hydrogen, halogen (fluorine, chlorine, iodine or bromine, but preferably chlorine or bromine) or OH; R_1 is hydrogen or C_1-C_4 alkyl; R_2 is hydrogen, C_1-C_4 alkyl (straight or branched-chain) or C_3-C_4 alkenyl; R_3 is hydrogen, C_1-C_6 alkyl (straight or branched-chain), C_3-C_6-cycloalkyl, methoxypropyl, C_3-C_4 alkenyl, phenyl, 2-hydroxyethyl, α,α-dimethylphenethyl or benzyl; and when R_2 and R_3 are taken together with the nitrogen to which they are attached, they may represent morpholino or N'-C_1-C_4 alkylpiperazino; R_4 is hydrogen, hydroxyl or OR_6; R_5 is hydrogen or C_1-C_4 alkyl; R_6 is C_1-C_6 alkyl; with the provisos that when R_3 is phenyl, 2-hydroxyethyl, α,α-dimethylphenethyl, cycloalkyl C_3-C_6, benzyl or methoxypropyl, R_2 is hydrogen; and when Z is OH, X and Y are hydrogen; and when Y is $NHCOR_5$, at least one of X and Z is hydrogen; and provided also that at least one of X,Y and Z represents a substituent other than hydrogen; racemic mixtures of the above-identified compounds and the optically active isomers and non-toxic, pharmacologically acceptable acid addition salts thereof.

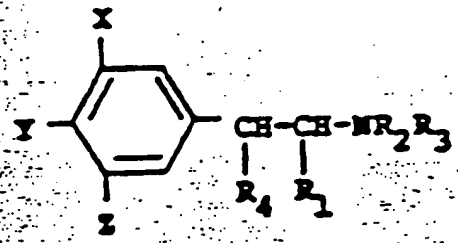
2. A method for the preparation of an animal feed composition comprising admixing an animal feed with from 0.01 to 400 grams per ton of feed of a compound of the following formula:



wherein X,Y,Z, R_1, R_2, R_3 and R_4 are as defined above.

3. A composition according to Claim 1 wherein the compound is 4-amino-α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol hydrochloride; 4-amino-3,5-dibromo-α-[(diisopropylamino)methyl]benzyl alcohol hydrochloride; 4-amino-3,5-dichloro-α-[(diisopropylamino)methyl]benzyl alcohol hydrochloride; 4-amino-3,5-dibromo-α-[(tert-butylamino)methyl]benzyl alcohol hydrochloride; 4-amino-3,5-dichloro-α-[(methylamino)methyl]benzyl alcohol hydrochloride; 4-amino-3,5-dichloro-α-[(isopropylamino)methyl]benzyl alcohol hydrochloride; 4-amino-3,5-dichloro-α-[(allylamino)-methyl]benzyl alcohol; α-[4-amino-3,5-dichlorophenyl]-4-mopholineethanol hydrochloride and 4-amino-3-bromo-α-[(tert-butylamino)methyl]-5-chlorobenzyl alcohol hydrochloride; α-[(tert-butylamino)methyl]-3,5-dichlorobenzyl alcohol hydrochloride.

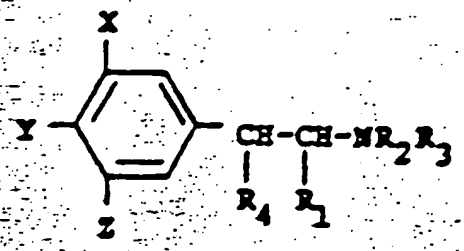
4. An animal feed supplement useful for enhancing the growth rate and for reducing the fat deposition in warm-blooded animals comprising from about 75% to 95% by weight of a compound of the following formula:



wherein X, Y, Z, R_1, R_2, R_3 and R_4 are as defined in Claim 1, above, and from about 5% to 25% by weight of a suitable carrier or diluent.

5. An injectable composition useful for enhancing the growth rate and for reducing the fat deposition in warm-

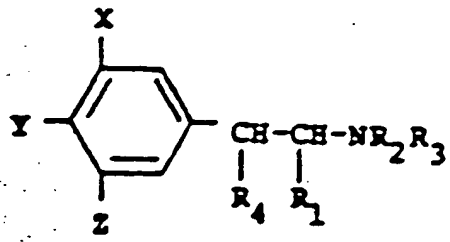
blooded animals comprising as an active ingredient a compound of the following formula:



wherein X, Y, Z, R_1, R_2, R_3 and R_4 are as defined in Claim 1, above, and a pharmaceutically acceptable carrier.

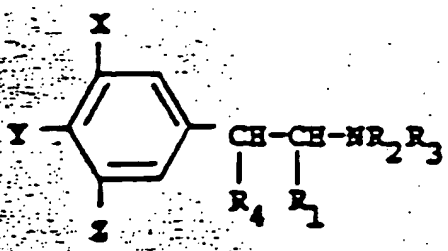
6. A composition according to Claim 5 wherein the active ingredient is present in an amount of from 0.001 to 50 mg/kg. of body weight.

7. An implant useful for enhancing the growth rate and reducing the fat deposition of meat-producing animals comprising as an active ingredient a compound of the following formula:



wherein X, Y. Z, R_1, R_2, R_3, and R_4 are as defined in Claim 1, above, and a pharmaceutically acceptable carrier.

8. A compound of formula:



wherein X is halogen;
Y is hydrogen or NH_2;
Z is halogen;
R_1 is hydrogen or C_1-C_4 alkyl;
R_2 is hydrogen, C_1-C_4 alkyl or C_3-C_4 alkenyl;
R_3 is hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, methoxypropyl, C_3-C_4 alkenyl, phenyl, 2-hydroxyethyl, α,α-dimethylphenethyl or benzyl; and when R_2 and R_3 are taken together with the

nitrogen to which they are attached, they may represent morpholino or N'-C_1-C_4 alkyl-piperazino; R_4 is hydroxy or OR_6; R_6 is C_1-C_6 alkyl; with the provisos that when Y is NH_2 then R_4 is OR_6; and when Y is hydrogen, R_2 is hydrogen; racemic mixtures of the above-identified compounds and the optically active isomers and non-toxic, pharmacologically acceptable acid addition salts thereof.

European Patent Office

EUROPEAN SEARCH REPORT

Application number EP 80 10 4619

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
D	US - A - 3 536 712 (J. KECK et al.) * Claim 1; column 32, lines 14-25; examples 202-205 *	1,4-7
X	ARZNEIMITTEL FORSCHUNG, (Drug Res.) vol. 26, no. 7a, July 1976, pages 1420-1427 Aulendorf, DE. H. UEBERBERG et al.: "Tierexperimentelle Untersuchungen zur Verträglichkeit von NAB 365 (Clenbuterol)" * Summary; page 1423, section 3.1.2; page 1425, section 3.2.2 *	1-7
X	NL - A - 246 478 (RADOUCO-THOMAS S.M-A) * Claims 1,12,15-17,19; page 4, lines 2-30; page 5, lines 1-7 *	1-7
	US - A - 3 818 101 (C.A. BAILE et al.) * Abstract; columns 1,2; column 7, lines 55-68; column 8, lines 1-68 *	1-7
X	GB - A - 1 141 606 (SOCIETE D'ETUDES DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES ET MEDICALES) * Claim 1 *	8

/.

CLASSIFICATION OF THE APPLICATION (Int. Cl.)

A 23 K 1/16
C 07 C 91/18
91/40
93/14

TECHNICAL FIELDS SEARCHED (Int. Cl.)

A 23 K 1/16
C 07 C 91/18
91/40
93/14
A 61 K 31/135
31/165

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	20-11-1980	GALLIGANI

EPO Form 1503.1 06.78

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.³)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	DE - A - 1 902 603 (C.H. BOEHRINGER & SOHN) * Claim 1; page 5, paragraph 4 * --	8	
X	GB - A - 1 218 135 (ABBOTT LABORATORIES) * Claim 1 * ----	8	TECHNICAL FIELDS SEARCHED (Int. Cl.³)

1053

533

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLORED OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☒ REPERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning documents *will not* correct images problems checked, please do not report the problems to the IFW Image Problem Mailbox